Review

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Dyspnea management in palliative care: current approaches and treatment strategies

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ABSTRACT

Dyspnea is a common and challenging symptom to manage in palliative care patients. This review discusses the pathophysiology, assessment methods, and current treatment approaches for dyspnea based on the existing literature. Both pharmacological (opioids, benzodiazepines, glucocorticoids) and non-pharmacological (oxygen therapy, respiratory therapy, environmental modifications) treatment strategies are examined in detail, with a discussion on their efficacy and potential side effects. This study is a narrative review compiling the current literature on the topic.

Keywords: Dyspnea, palliative care, symptom management, multidisciplinary approach

INTRODUCTION

Dyspnea is a complex respiratory symptom with distinct sensory components that is individually perceived.[1] Commonly encountered in palliative care patients, this condition arises from interactions among the respiratory, cardiovascular, and neurological systems. Dyspnea is not merely a physical symptom but a complex condition involving psychological and emotional dimensions. Effective management of dyspnea, which significantly impacts patients' quality of life, is a fundamental goal in palliative care practices. The diagnosis and management of dyspnea vary according to the patient's clinical condition and the progression of the disease. Moreover, dyspnea is a significant source of stress for both patients and their caregivers, making it a complex symptom that requires a multidisciplinary approach.

PREVALENCE OF DYSPNEA

Dyspnea is one of the most common symptoms negatively affecting the quality of life in patients with advanced-stage diseases. Studies indicate that dyspnea is prevalent among patients with terminal-stage cancer, chronic obstructive pulmonary disease (COPD), heart disease, AIDS, or kidney disease.[2-5] The frequency and severity of the symptom increase during the final months of life, causing significant discomfort for patients.[6,7] In the course of chronic diseases, the management of dyspnea requires consideration of both its physiological and psychosocial components.

PATHOPHYSIOLOGY

Dyspnea is a multidisciplinary symptom that arises from the complex interactions between the central nervous system, the respiratory and cardiovascular systems, and psychological factors.[1] The neurophysiological control of respiration is regulated through the respiratory centers in the medulla oblongata, which receive inputs from peripheral chemoreceptors (carotid bodies and aortic bodies), central chemoreceptors, and mechanoreceptors.[8] Dyspnea can develop as a result of dysfunctions in one or more of these mechanisms.

The perception of dyspnea can be described by patients in various ways, such as "air hunger," "increased breathing effort," or "chest tightness." These different perceptions reflect the diversity of underlying pathophysiological mechanisms. These mechanisms include:

Mechanical Load and Muscle Fatigue

The respiratory muscles, including the diaphragm, intercostal muscles, and accessory respiratory muscles, perform the essential mechanical function of maintaining ventilation. However, excessive loading or functional insufficiency of these muscles can impair adequate ventilation, leading to dyspnea. For instance, in pulmonary fibrosis, despite increased effort by the respiratory muscles due to reduced lung compliance, sufficient tidal volume cannot be achieved, contributing to dyspnea development.

Gas Exchange Impairments

Gas exchange in the lungs is maintained through the balance between alveolar ventilation, diffusion capacity, and perfusion. Conditions such as hypoxia or hypercapnia enhance respiratory drive, triggering the sensation of dyspnea.[9] For example, in pulmonary embolism, ventilation

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remains intact, but perfusion is disrupted, leading to hypoxia and the subsequent onset of dyspnea.

Cardiogenic Factors

Dyspnea is not solely limited to respiratory pathologies but is also associated with cardiovascular diseases such as heart failure.[10] Cardiac-origin dyspnea typically arises due to increased pulmonary capillary pressure secondary to pulmonary congestion. Elevated pulmonary venous pressure leads to interstitial edema and alveolar fluid accumulation, impairing gas exchange. Even in the absence of hypoxia, these mechanisms can trigger the sensation of dyspnea.

Airway Resistance and Flow Limitation

Increased airway resistance contributes to greater respiratory effort during both inspiration and expiration, resulting in dyspnea. In conditions such as asthma and COPD, airway inflammation and narrowing restrict airflow, particularly during expiration, thereby increasing respiratory workload and promoting dyspnea.

Psychological and Neurological Mechanisms

Dyspnea is a complex sensory experience processed within the central nervous system. The cortical perception of breathlessness arises from the integration of respiratory center signals from the brainstem with processing in brain regions such as the insula, anterior cingulate cortex, prefrontal cortex, and amygdala.[11] This process is influenced not only by respiratory and cardiovascular inputs but also by emotional and cognitive factors. Notably, the amygdala, which is associated with anxiety and fear responses, can heighten the perception of dyspnea, leading patients to experience respiratory distress more intensely.[12] Consequently, effective dyspnea management should not only involve mechanical and pharmacological interventions but also incorporate strategies targeting cognitive and psychological factors.

The causes of dyspnea and its pathophysiological mechanisms are presented in Table 1.

Table 1. Pathophysiological classification of diseases causing dyspnea

Category	Diseases/conditions	Primary mechanism
Obstructive	COPD, asthma, bronchiectasis, central airway obstruction	Airflow limitation, airway inflammation
Restrictive	Pulmonary fibrosis, thoracic deformities, neuromuscular diseases	Decreased lung compliance, respiratory muscle weakness
Cardiogenic	Heart failure, pulmonary hypertension, myocardial infarction	Pulmonary congestion, reduced cardiac output
Psychogenic	Anxiety, panic disorder	Hyperactivity of the respiratory control center
Mechanical	Diaphragmatic paralysis, chest wall deformities	Respiratory muscle dysfunction
Hematologic	Anemia, carbon monoxide poisoning	Decreased oxygen-carrying capacity
Vascular	Pulmonary embolism, pulmonary hypertension	Perfusion impairment, right ventricular failure

ASSESSMENT

The assessment of dyspnea aims to determine the severity of the symptom, the progression of the underlying disease, and its impact on the patient's quality of life. Patients may describe dyspnea in various ways, making it essential to consider their individual experiences during the clinical evaluation. Common assessment methods include numerical rating scales, visual analog scales, and functional assessment tools. The Memorial Symptom Assessment Scale and the Edmonton Symptom Assessment Scale are frequently used in clinical practice.[13,14] Evaluating changes in patients' functional capacities and daily activities provides valuable insights into dyspnea management. Key aspects of the clinical evaluation include how patients describe their dyspnea, the timing of its onset, and the conditions under which it occurs.

PSYCHOLOGICAL IMPACTS OF DYSPNEA

Dyspnea is not merely a physical symptom but also exerts significant psychological and social effects on patients.[15] It is commonly associated with anxiety, depression, and social isolation, which can subsequently lower the patient's quality of life. Particularly in advanced-stage patients, the sensation of breathlessness is often linked to a sense of proximity to death, leading to heightened anxiety and panic attacks.[16] Anxiety can exacerbate the severity of dyspnea by increasing respiratory effort. Therefore, psychosocial support and anxiety management should be integrated into the treatment process. Psychological support is a crucial component of the patient-centered care approach in palliative care settings.[17] For these reasons, dyspnea management must address not only the physical symptoms but also the psychosocial needs of the patient.

TREATMENT AND MANAGEMENT

The primary goal of dyspnea treatment is to alleviate the patient's discomfort and improve their quality of life. An integrated strategy involving both pharmacological and non-pharmacological approaches is essential. Treatment options should be tailored based on the patient's clinical condition, symptom severity, and underlying diseases.

Targeted Treatments Addressing Underlying Causes of Dyspnea

In dyspnea management, alongside symptomatic approaches, targeted treatments addressing underlying causes can also be implemented.[18] Identifying various etiological factors such as COPD, central airway obstruction, heart failure, lymphangitic carcinomatosis, and malignant pleural effusions allows for the individualization of treatment strategies.

MANAGEMENT

COPD and Dyspnea Management

COPD is one of the most common conditions leading to dyspnea and is frequently observed in advanced cancer patients, particularly those with a history of smoking. In this patient group, the assessment and management of airway obstruction are of critical importance. While bronchodilator

therapy can provide symptomatic relief, pulmonary rehabilitation programs—aimed at improving exercise tolerance and offering psychosocial support—can enhance patients' quality of life. However, for patients with a limited life expectancy, the effectiveness of pulmonary rehabilitation may be restricted.

Idiopathic Pulmonary Fibrosis and Dyspnea Management

Despite having a worse prognosis compared to many malignancies, patients with idiopathic pulmonary fibrosis (IPF) often do not receive adequate palliative care. In a study conducted by Arı et al.[19], the mortality rate of patients treated in intensive care due to an acute exacerbation of IPF was reported to be 62.7%. Similarly, a survey conducted by Akiyama et al.[20] among pulmonologists revealed that providing palliative support to patients with IPF posed greater challenges compared to lung cancer patients. These findings highlight the necessity of developing and prioritizing specialized palliative care programs tailored for patients with IPF.

Lung Malignancies and Dyspnea Management

Lung malignancies can lead to the development of dyspnea, particularly in advanced stages.[18] The primary mechanisms contributing to dyspnea in lung cancer include airway obstruction due to tumor burden, pleural effusion, lymphangitic carcinomatosis, superior vena cava syndrome, and lung injury secondary to radiation or chemotherapy.[21] In the management of dyspnea associated with lung malignancies, both symptomatic approaches and treatments targeting the underlying disease are crucial.

Airway obstruction due to tumor burden: Endobronchial tumors can be debulked using bronchoscopic techniques such as laser therapy, electrocautery, argon plasma coagulation, and cryotherapy.

Pleural effusion: Symptomatic relief can be achieved through therapeutic thoracentesis, placement of a pleural catheter, or pleurodesis.

Lymphangitic carcinomatosis: Glucocorticoids and diuretics may help control symptoms.

Superior Vena Cava Syndrome: Radiotherapy, chemotherapy, or intravascular stent placement can improve venous return and alleviate dyspnea.

In cases of dyspnea caused by central airway obstruction, glucocorticoids can enhance airflow through their tumor-reducing effects.[22] Techniques such as endobronchial laser, electrocautery, argon plasma coagulation and cryotherapy can be used to reduce tumor tissue and provide palliative respiratory support with airway stents. However, careful evaluation is necessary to ensure that such invasive interventions align with the patient's overall care goals.

In patients with end-stage heart failure, dyspnea may develop due to pulmonary congestion, where diuretic therapy can be beneficial. Similarly, in cases of lymphangitic carcinomatosis, diuresis and glucocorticoids have been reported to provide symptomatic relief.[23] Malignant pleural effusions are another significant cause of dyspnea, and treatment options include therapeutic thoracentesis, placement of an indwelling pleural catheter, pleurodesis, and, in rare cases, pleuroperitoneal shunt procedures.

Additionally, glucocorticoids can be used in the management of various causes of dyspnea, including COPD exacerbations, superior vena cava syndrome, radiation pneumonitis, and chemotherapy-induced pneumonitis.[24] In this context, determining individualized treatment approaches targeting the underlying cause of dyspnea is crucial for optimizing symptom control and improving patients' quality of life.

TREATMENTS

Various interventions are utilized in clinical practice to alleviate dyspnea. These include non-pharmacological approaches such as multidimensional dyspnea management programs, graded exercise therapy, increased airflow, breathing techniques, and supplemental oxygen, alongside pharmacological treatments like opioids.[25]

Pharmacological Treatments

Use of opioids in dyspnea management: Opioids play an important role in the management of dyspnea in palliative care.[26] Their use in dyspneic patients reduces respiratory effort, facilitating easier breathing. Opioids act on the central nervous system, decreasing the perception of dyspnea and providing a sense of respiratory comfort. Studies have demonstrated that opioids are effective in alleviating dyspnea during the terminal stages of cancer and chronic diseases.[18]

Opioid dosages and administration methods: Opioids can be administered orally, subcutaneously, or intravenously for the treatment of dyspnea. The dosage and route of administration are determined based on the severity of the patient's symptoms and their tolerance to opioids:

- **Initial dose for patients not using opioids:** Oral morphine 5 mg every 4 hours can be initiated, with additional 2.5 mg rescue doses as needed. Alternatively, for subcutaneous administration, 2.5-3 mg of morphine every 4 hours can be given.
- **Dose adjustment for opioid-tolerant patients:** The dosage may be increased by 25-50% based on the patient's current opioid use.
- **For severe dyspnea crises:** IV morphine can be administered at 2.5-5 mg doses, repeated every 15-30 minutes if necessary.
- **For long-term use:** The total daily dose should be calculated based on the patient's regular daily opioid intake and individualized accordingly.

Side Effects and Precautions of Opioids

The most common side effects of opioids include sedation, constipation, nausea, and respiratory depression.[27]

While opioids are effective in the management of dyspnea, they may pose a risk of respiratory depression in patients receiving high doses or those with opioid sensitivity.[28] Respiratory depression manifests as a respiratory rate of <8–10 breaths per minute, hypoventilation, a significant drop in oxygen saturation, and hypercapnia. Therefore, regular

respiratory assessment is essential in patients receiving opioid therapy. This assessment can be performed as follows:

- **For low-risk patients:** Monitoring respiratory rate and pulse oximetry may be sufficient.
- **For moderate-to-high-risk patients:** Capnography (end-tidal CO_2 monitoring) can be used for early detection of hypoventilation.

In cases of opioid-induced respiratory depression, opioid antagonists such as naloxone may be administered. However, naloxone reverses all opioid effects, necessitating careful dose titration, particularly in palliative care patients.[29] The recommended naloxone administration doses are as follows:

- **Mild-to-moderate respiratory depression:** 0.04 mg IV slow infusion, titrated every 2–3 minutes as needed.
- **Severe opioid toxicity:** 0.1–0.2 mg IV, repeated every 2–3 minutes as necessary until the patient stabilizes.
- **Alternative administration:** 0.4 mg IM/SC.
- **Low-dose infusion (0.25–1 mcg/kg/hour):** Preferred to reverse respiratory depression without completely eliminating opioid analgesia.

Preventive strategies are crucial for enhancing the safety of opioid therapy in patients at risk of respiratory depression. Initiating treatment with low opioid doses and gradually titrating the dose is recommended. Additionally, selecting opioids with a lower respiratory depressant effect rather than those with high sedative potency may reduce the risk. Opioid rotation can be considered as an alternative strategy in patients who develop tolerance or experience adverse effects. Furthermore, multimodal analgesia strategies should be adopted whenever possible to minimize naloxone requirements, integrating non-opioid analgesics into the treatment plan.

The major side effects of opioids and their management protocols are presented in Table 2.

Table 2. Most common side effects of opioids and their management

Side effect	Prevention/management strategy
Constipation	Regular use of laxatives (lactulose, senna, macrogols). Agents that enhance peristalsis are preferred.
Nausea/vomiting	Metoclopramide (10 mg, three times daily) or ondansetron (4–8 mg, twice daily) can be used. Nausea typically resolves within the first few days after opioid initiation.
Sedation	Dose reduction or switching to an alternative opioid may be considered. The lowest effective dose should be targeted to maintain the patient's functional capacity.
Respiratory depression	Opioid titration should be performed carefully. In cases of severe respiratory depression, naloxone (0.1–0.2 mg IV, repeated as needed) can be administered.
Pruritus	Antihistamines (diphenhydramine or hydroxyzine) may be used. Alternative opioid selection should be considered if necessary.
Urinary retention	Dose reduction or catheterization may be considered if required.

Although morphine is the most commonly used opioid, alternatives such as fentanyl, oxycodone, hydromorphone, and methadone can also be considered.[30,31]

Use of Methadone in Dyspnea Management

Methadone is an opioid with unique pharmacological properties that can be used as an alternative in dyspnea management. In addition to acting as a μ-opioid receptor agonist like conventional opioids, it also functions as an N-methyl-D-aspartate (NMDA) receptor antagonist and a serotonin-norepinephrine reuptake inhibitor.[32]

Advantages of Methadone[33]

Use in opioid rotation: Methadone can be considered an alternative for patients who do not achieve adequate symptomatic relief with other opioids.

Reduction of opioid tolerance: Due to its NMDA receptor antagonism, methadone may provide efficacy at lower doses in patients who have developed opioid tolerance.

Effects on neuropathic pain and dyspnea: NMDA receptor blockade can reduce neuropathic pain and opioid-induced hyperalgesia, which may help alleviate dyspnea perception in chronic illnesses.

Risk of respiratory suppression: Compared to morphine, methadone may cause less respiratory depression; however, due to its long half-life, careful dose titration is required.

The dosage and administration of methadone should be carefully tailored to the patient's opioid tolerance and clinical condition. For opioid-naïve patients, the recommended starting dose is 2.5 mg orally every 8–12 hours. In cases requiring opioid rotation, when transitioning from morphine to methadone, the morphine equivalent dose should be calculated at 10–20% of the morphine dose, with careful titration. Due to methadone's long half-life, dose adjustments should not be made sooner than 5–7 days to prevent cumulative effects and minimize adverse reactions.

There are several key factors to consider when using methadone. First, due to the risk of cumulative effects, dose titration should be conducted cautiously, and sudden dose increases should be avoided. Methadone is known to prolong the QT interval and may lead to cardiac arrhythmias; therefore, ECG monitoring is recommended, especially during long-term use. Additionally, potential drug interactions with other sedative medications should be considered, and patients should be closely monitored. These precautions are essential for ensuring the safe and effective use of methadone in dyspnea management.

Benzodiazepines

These can be used to reduce anxiety associated with dyspnea. Anxiety can contribute to the exacerbation of dyspnea symptoms, and in such cases, managing anxiety can help alleviate dyspnea. Benzodiazepines are often used as supportive therapy in patients experiencing dyspnea accompanied by anxiety.[34] However, in the absence of an anxiety component, benzodiazepines are not recommended as a routine treatment strategy for dyspnea management.[35]

Glucocorticoids

Corticosteroids are one of the pharmacological agents frequently used in palliative care for managing dyspnea in cancer patients. They can improve respiratory function by reducing inflammation, particularly in conditions such as malignant airway obstruction, lymphangitic carcinomatosis, pulmonary inflammation, and radiation pneumonitis.[24] The anti-inflammatory and membrane-stabilizing effects of corticosteroids contribute to the alleviation of dyspnea symptoms by reducing airway edema and mucosal inflammation. In clinical practice, one of the most commonly used agents is dexamethasone, which is typically administered at a dose of 4–8 mg/day. However, long-term use of corticosteroids can lead to side effects such as hyperglycemia, muscle weakness, and immunosuppression, necessitating careful patient selection and individualized dose adjustments. Although current evidence on the effectiveness of corticosteroids in dyspnea management is limited, short-term use in selected patient groups has been reported to provide symptomatic relief.[36] Therefore, corticosteroid therapy is considered a supportive option that should be carefully evaluated in palliative care patients.

Oxygen Therapy

Oxygen therapy is an essential treatment modality used to alleviate dyspnea and potentially prolong survival in hypoxemic patients.[18] The effectiveness of long-term oxygen therapy (LTOT) varies depending on the underlying disease and the degree of hypoxemia. In COPD, LTOT is the only treatment that has been shown to improve survival in patients with a resting $PaO_2 \leq 55$ mmHg or $SaO_2 \leq 88\%$.[37] However, the efficacy of oxygen therapy in managing dyspnea in non-hypoxemic patients remains limited. Therefore, while oxygen therapy can provide significant benefits in hypoxemic individuals, it is important to recognize that unnecessary oxygen administration in normoxemic patients has minimal impact.[38]

Limitations of Noninvasive Ventilation in Palliative Use

Noninvasive ventilation (NIV) is widely used in clinical settings outside of palliative care, particularly for the management of hypercapnic respiratory failure. In patients with hypercapnic respiratory failure ($PaCO_2$ >45 mmHg, pH <7.35) during COPD exacerbations, NIV reduces the workload of the respiratory muscles, decreasing the need for mechanical ventilation and reducing mortality.[39]

Respiratory distress is commonly observed in individuals with terminal or progressive diseases, such as cancer, advanced COPD, amyotrophic lateral sclerosis, and IPF.[40,41] In these complex clinical scenarios, NIV may be preferred to provide respiratory support without resorting to invasive methods like intubation or invasive mechanical ventilation.[42] NIV involves the application of positive pressure ventilation through noninvasive interfaces, such as nasal masks, facial masks, or nasal plugs, instead of invasive airway devices like endotracheal tubes or tracheostomies.[43] The 2017 guidelines issued by the European Respiratory Society and the American Thoracic Society emphasize the support for palliative use of NIV in dyspnea patients with terminal cancer and other advanced diseases.[44] Accordingly, NIV is recommended as a palliative intervention in patients experiencing severe dyspnea who prioritize comfort-focused measures over aggressive life-prolonging treatments.[45] However, further evidence is needed to establish the effectiveness and clinical benefits of NIV in this patient population.

Non-Pharmacological Methods

- **Respiratory therapy:** Patients can be taught breathing exercises.
- **Breathing techniques:** Diaphragmatic breathing and controlled breathing techniques may provide relief.
- **Environmental adjustments:** Proper ventilation of the patient's living space, humidity control, and appropriate positioning can help alleviate symptoms.

Dyspnea Crisis and Palliative Sedation

Dyspnea crises are characterized by sudden and severe episodes of breathlessness, often occurring in the terminal stage of life.[46] In such situations, the patient's distress can be alleviated through the use of opioids, benzodiazepines, and, if necessary, palliative sedation. Palliative sedation should be considered as an option for managing refractory symptoms.

Definition and Initiation Criteria of Palliative Sedation

Palliative sedation is the controlled reduction of a patient's consciousness to relieve refractory symptoms that cannot be managed with conventional treatments. According to the European Association for Palliative Care (EAPC) guidelines, palliative sedation should only be administered when the following criteria are met:[47]

- **Presence of refractory symptoms:** Symptoms such as pain, dyspnea, delirium, anxiety, or other distressing conditions must remain unmanageable despite all available medical and pharmacological interventions.
- **End-of-life stage:** Palliative sedation is typically indicated in the terminal phase of illness (patients with a life expectancy of days or hours).
- **Patient or surrogate consent:** In cognitively intact patients, informed consent should be obtained; in unconscious patients, legal representatives should be involved in decision-making.
- **Multidisciplinary decision-making:** The decision should be evaluated by physicians, nurses, ethics committees, and the patient's family to ensure a holistic approach.
- **No intention to hasten death:** The primary aim of palliative sedation is symptom relief, and it should not be confused with euthanasia or assisted suicide.

Pharmacological Approach

The most commonly used agents in palliative sedation are benzodiazepines, neuroleptics, and barbiturates. Among these:[47]

- **Midazolam:** For mild sedation, an initial dose of 2.5 mg SC or 1.25 mg IV is recommended; for deep sedation, an initial dose of 5–10 mg SC or 2.5–5 mg IV is used. The maintenance dose is 1 mg/hour, which can be adjusted based on clinical response.
- **Phenobarbital:** Can be administered parenterally at 37.5–150 mg/day or rectally at 75–300 mg/day.

Palliative Sedation and Ethical Considerations

While palliative sedation is intended to alleviate symptoms, it may pose ethical concerns regarding its potential to hasten death. Therefore, the following aspects should be carefully considered:

- **Patient autonomy:** If the patient is conscious, they should be actively involved in decision-making; if not, the legal representatives should participate in the process.
- **End-of-life-specific application:** There is ongoing debate on whether palliative sedation should be restricted to the terminal phase. Some experts argue that sedation should focus on symptom control rather than life expectancy.
- **Multidisciplinary approach:** The decision to initiate sedation should involve ethics committees and palliative care specialists to ensure optimal patient care.

In conclusion, for palliative sedation to be implemented effectively and ethically, the patient's individual needs should be considered, the treatment process should be managed by a multidisciplinary team, and comprehensive information about the procedure should be provided to the patient and their family.

CONCLUSION

Dyspnea is a common symptom in palliative care patients that requires effective management. While current treatment approaches play a significant role in symptom control, several aspects require further investigation. The long-term efficacy and side effect profile of opioids, the potential benefits of methadone in dyspnea management, and the impact of long-term oxygen therapy on survival and quality of life need to be more clearly defined. Additionally, more comprehensive studies are required on patient selection criteria and the ethical aspects of palliative sedation. Future research will contribute to the development of more effective and patient-centered approaches in dyspnea management.

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Referee Evaluation Process

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The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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